Medical and Pediatric Oncology 26:54–56 (1996)

Familial Sideroblastic Anemia With Emergence of Monosomy 5 and Myelodysplastic Syndrome

G. Kardos, MD, PhD, A.J.P. Veerman, MD, PhD, F.C. de Waal, MD, PhD, L.J. van Oudheusden, MD, and R. Slater, PhD

The case history of two sisters with pyridoxine-refractory familial sideroblastic anemia (FSA) is presented in which one developed a myelodysplastic syndrome (MDS) with monosomy for chromosome 5. Bone marrow examination of both patients at diagnosis showed erythroid hyperplasia with more than 50% ring sideroblasts. Karyotypic analysis initially showed a normal 46, XX karyotype in both of the children. Therapeutic trials with pyridoxine, prednisone, and erythropoietin were unsuccessful. The first patient required regular transfusions and developed a significant hemosiderosis. At the age of 9 years, 7.5 years after the diagnosis of FSA, refractory anemia with excess of blasts (RAEB) was diagnosed. Bone marrow cytogenetic analysis revealed a clone with monosomy for chromosome 5. Her sister's illness was detected at the age of 12 years. She has a more benign course of disease, remains largely transfusion independent and until now shows no signs of myelodysplasia. To our knowledge this is the first observation of a transition of FSA to MDS accompanied by the appearance of a chromosomal abnormality. FSA might be another type of bone marrow failure syndrome, therefore close follow-up of these patients may be necessary.

Key words: familial sideroblastic anemia, myelodysplastic syndrome, monosomy 5

INTRODUCTION

Sideroblastic anemias (SA) are classified as inherited or acquired. It is a heterogeneous group of disorders, usually characterized by microcytic hypochromic anemia, bone marrow erythroid hyperplasia with ringed sideroblasts, and increased serum ferritin level as signs of ineffective erythropoiesis [1]. Inherited or familial sideroblastic anemia (FSA) is usually an X-linked disease affecting males, but autosomal recessive inheritance is also observed [2]. It may be pyridoxine-responsive or refractory. While idiopathic acquired sideroblastic anemia is included among the myelodysplastic syndromes, the inherited forms are now known to predispose to malignant transformation.

This report describes two sisters with different course of FSA; in one a myelodysplastic syndrome (MDS) with monosomy for chromosome 5 developed.

CASE REPORTS

Patient 1

This previously healthy 18-month-old girl presented with severe microcytic anemia. Apart from moderate hepatosplenomegaly and marked pallor, physical examination was unremarkable. Laboratory evaluation revealed the following: hemoglobin 2.4 mmol/L, MCV 70 fl, MCHC 19 mmol/L, MCH 1304 amol/L, leukocytes 7.2×10^9/L with 26% segmented neutrophils, 68% lymphocytes, 6% monocytes, platelets 247×10^9/L, reticulocytes 0.4%, ferritin 214 μg/L. The hemoglobin profile showed 0.8% HbF and 2.2% HbA_2. Red cell morphology—except of a slight polychromatophilia—was normal. Examination of the bone marrow revealed prominent erythroid hyperplasia with a shift to the left in the erythroid line but no signs of dyserythropoiesis was seen. Iron staining showed increased iron storage, 60% of the erythroid cells were ringed sideroblasts. Myeloid cells and megakaryocytes were morphologically normal. Cytogenetic studies of the bone marrow revealed a normal female karyotype: 46, XX [43]. A thorough family investigation was not possible, but family history indicated no

From the Department of Pediatrics, Free University Hospital, Amsterdam (G.K., A.J.P.V., F.C.d.W.), Westfries Gasthuis, Hoorn (L.J.v.O.), and the Institute of Human Genetics, Academic Medical Centre, Amsterdam (R.S.), The Netherlands.

Received December 13, 1994; accepted May 9, 1995.

Address reprint requests to G. Kardos, M.D., Department of Pediatrics, Free University Hospital, De Boelelaan 1117, Postbus 7057, 1107 MB Amsterdam, The Netherlands.

consanguinity or a history of known anemia. The parents did not give consent to investigate their other daughter or themselves, thus no evaluation of the hereditary nature of the disease was possible. The diagnosis of SA was established, the patient received a blood transfusion, and pyridoxine treatment (5 mg/kg daily) was started. However, the patient proved to be pyridoxine unresponsive, thus after 4 months of therapy it was stopped. Later prednisone and erythropoietin were also tried but without success. She received transfusions at a frequency of one per month. Serum ferritin level rose gradually despite the early initiation of subcutaneous desferrioxamine therapy. Reevaluation of the disease at the age of 9 years revealed a pale, slightly pigmented girl with a frontal bossing. Her growth was satisfactory, height and weight were both at the 50th percentile. The liver was palpable 3 cm, the spleen 6 cm below the costal margin. Laboratory examinations showed the following: hemoglobin 3.2 mmol/L, MCV 82 fl, MCHC 19 mmol/L, MCH 1488 amol/L, reticulocytes 0.4% plateletes 151×10^9/L, leukocytes 2.0×10^9/l with 2% eosinophiles, 27% neutrophils, 66% lymphocytes, and 5% monocytes. Liver function tests were normal, serum ferritin was 3,770 μg/L. A bone marrow biopsy showed a hyperplastic bone marrow with erythroid hyperplasia and strikingly increased reticulin. More than 90% of the erythroblasts were ringed sideroblasts. The majority of the erythroblasts had dyserythropoietic features, bi- and multinuclearity, irregular nuclear shape, and abnormal nuclear lobulation was seen. The number of megakaryocytes was increased with a predominance of micromegakaryocytes. An increase of myeloblasts up to 20% of the myeloid cells was also seen. A part of the myeloid cells contained abnormal or absent granulation. The diagnosis of refractory anemia with excess of blasts (RAEB) was established. The result of chromosome analysis of the bone marrow cells revealed two clones, in 36 cells a normal 46, XX karyotype was seen, seven cells showed however, a 45, XX, −5 aberration. In the last 6 months, her condition has remained stable and she still receives monthly transfusions. A matched unrelated bone marrow transplantation is planned.

Patient 2

She is the older sister of patient 1. She was first seen at the age of 12 years because of marked pallor and fatigue. Her height and weight were on the 75th percentile, menarche age 11.5 years. Her liver was enlarged 2 cm below the costal margin, no splenomegaly was found. Laboratory studies revealed the following: hemoglobin 4.6 mmol/L, MCV 70 fl, MCHC 20 mmol/L, MCH 1460 amol/L, reticulocytes 6.9%, platelets 495×10^9/L, leukocytes 5.6×10^9/L with 1% eosinophils, 26% neutrophils, 67% lymphocytes, and 6% monocytes, ferritin 144 μg/l, HbA_2 2.1%, HbF 0.5%. Examination of the bone marrow revealed prominent erythroid hyperplasia with marked predominance of young erythroblasts without dyserythropoietic features. Intracellular iron was found to be increased and more than 90% of the erythroblasts were ringed sideroblasts. Cytogenetic studies of the bone marrow revealed a normal female karyotype, 46 XX [39]. Detailed family studies were again refused. The probable diagnosis of FSA—taking into consideration the disease of her sister—of the autosomal recessive type was made. A 3-month trial with Pyridoxine (3 mg/kg daily) was tried without effect. In the following years, the hemoglobin level stayed stable around 5 mmol/L and no transfusions were necessary. Serum ferritin remained between 200 and 300 μg/L without desferrioxamine therapy. At an evaluation 5 years later, except for a moderate hepato-splenomegaly, physical examination was unremarkable. Laboratory data showed the following: hemoglobin 5.4 mmol/L, MCV 69 fl, MCHC 19 mmol/L, MCH 1,250 amol/L, reticulocytes 3.2%, platelets 530×10^9/L, leukocytes 5.9×10^9/L with 2% eosinophils, 1% basophils, 47% neutrophils, 48% lymphocytes, ferritin 284 μg/L. A bone marrow aspirate revealed hyperplastic marrow with a marked erythroid predominance. The erythrocytes showed dyserythropoietic features; double and multinuclear cells and irregular cytoplasmic structure were seen. Myeloid precursors and megakaryocytes appeared normal. Cytogenetic analysis again showed a normal female karyotype, 46 XX [34].

DISCUSSION

Sideroblatic anemias are a heterogeneous group of hyperproliferative anemias. They share a common morphological feature, namely ringed sideroblasts in the bone marrow. The basic defect in this sort of anemia is thought to be a defective heme biosynthesis leading to impaired utilization of iron by the erythroblasts [3].

Sideroblastic anemias are classified as inherited or acquired. The hereditary forms are usually transmitted as X-linked traits but rare forms of autosomal recessive disease have been documented. Mutations on different sites of the ALAS2 gene or at another locus on chromosome X have been found. In Pearson's syndrome—a sideroblastic anemia with pancreatic fibrosis and bone marrow vacuolization—an inherited mitochondrial deletion has been reported [2,4]. Pyridoxine unresponsive patients often require regular transfusions to maintain adequate hemoglobin levels, which is the main reason for massive iron accumulation. Sometimes patients not receiving transfusions also develop hemosiderosis which affects the liver, heart, and endocrine organs [5]. Cardiac and liver failure are the most common causes of death in these patients. In severe forms of the disease allogenic bone marrow transplantation has been tried with varied success [6,7].

Acquired sideroblastic anemias are classified as secondary or primary. Secondary acquired SA arise due to the effect of various toxic substances on the bone marrow

such as alcohol, antituberculous agents, or chloramphenicol. This form of anemia can usually be reversed by elimination of the toxic agent.

Primary acquired SA is a myelodysplastic disorder and the ring sideroblasts in this disease are merely a phenotypic manifestation of an underlying stem cell disorder affecting multiple lineages. MDS usually occurs in elderly patients and is relatively rarely seen in children. While Creutzig et al. estimates the frequency to be approximately 1%, Hasle reports a 9% incidence of all malignancies in children [8,9]. Cancer chemotherapy, especially alkylating agents and therapeutic irradiation can cause MDS in children [10]. A number of rare genetic diseases diagnosed in the first years of life (e.g., Fanconi's anemia, ataxia telangiectasia, neurofibromatosis type I, Schwachmann's syndrome, Bloom's syndrome, xeroderma pigmentosum, etc.) are known to predispose to hematological malignancies and MDS [11]. The monosomy 7 syndrome and its familial variant comprise a common form of MDS in the young [12]. In contrast to the occasionally indolent course of adults, MDS is always highly malignant in children, therefore aggressive therapy including allogeneic bone marrow transplantation is indicated [13].

Our patients have pyridoxine unresponsive FSA. Patient 1 appeared to be transfusion dependent and developed symptoms of massive iron overload. Her older sister, patient 2, received only a few transfusions and had a relatively benign course of the disease. This different course of the disease in unrelated patients is well described but the underlying cause of the difference is unknown [14]. Both our patients initially had a normal bone marrow karyotype in accordance with the observations of others [15]. Patient 1 developed symptoms of MDS 7 years after the diagnosis of the FSA. Karyotypic examination revealed the occurrence of monosomy 5. Her sister's findings remained unchanged except for dyserythropoietic features in the bone marrow.

Monosomy 5 is not a typical feature of de novo childhood MDS but is often seen in therapy related MDS [15]. We found no exposure to a toxic agent which could have been responsible for the occurrence of monosomy 5. Pyridoxine, prednisone, and erythropoietin which were used unsuccessfully in our patient are not known to induce this transformation, on the contrary, they are used in therapeutic settings to treat MDS [9]. Although rare pediatric constitutional syndromes have an excess risk to develop into MDS, FSA is not considered to be one of them [16].

FSA is a very rare disease and no large series of patients has been published. Children suffering from the serious form of the disease inevitably die as a result of iron overload. Probably due to the lack of adequate chelation therapy, too few patients have survived until the age when malignant transformation could occur. According to our observations, FSA might be considered as another type of bone-marrow-failure syndrome with an increased risk for development of MDS. Patients should be carefully monitored not only for evidence of iron overload but for signs of myelodysplasia.

REFERENCES

1. Bridges KR: Iron metabolism and sideroblastic anemia. In Nathan D, Oski F (eds): "Hematology of Infancy and Childhood." Philadelphia: WB Saunders, 1993, pp. 391–412.
2. Jardine PE, Cotter PD, Johnson SA, Fitzsimons EJ, Tyfield L, Lunt PW, Bishop DF: Pyridoxine refractory congenital sideroblastic anaemia with evidence for autosomal inheritance: exclusion of linkage to ALAS2 at Xp11.21 by polymorphism analysis. J Med Genet 31:213–218, 1994.
3. Cazzola M, Barosi G, Bergamaschi G, Dezza L, Palestra P, Polino G, Ramella S, Spriano P, Ascari E: Iron loading in congenital dyserythropoietic anaemias and congenital sideroblastic anaemias. Br J Haematol 54:649–654, 1983.
4. Nusbaum NJ: Concise review: genetic bases of sideroblastic anemia. Am J Hematol 37:41–44, 1991.
5. Harris JW, Danish E, Brittenham GM, McLaren CE: Pyridoxine responsive hereditary sideroblastic erythropoiesis and iron overload: two microcytic subpopulations in the affected male, one normocytic and one microcytic subpopulation in the obligate female carrier. Am J Hematol 42:400–401, 1993.
6. Urban C, Binder B, Hauer C, Lanzer G: Congenital sideroblastic anemia successfully treated by allogenic bone marrow transplantation. Bone Marrow Transpl 10:373–375, 1992.
7. Castenada VL, Williams TE, Harper JL, Graham-Pole J, Parmley RT: Severe refractory anemia with ringed sideroblasts and bone marrow aplasia in a child. Am J Pediatr Hematol Oncol 14:70–76, 1992.
8. Creutzig U, Cantu-Rajnoldi A, Ritter J, Romitti L, Odenwald E, Conter V, Riehm H, Masera G: Myelodysplastic syndromes in childhood. Report of 21 patients from Italy and West-Germany. Am J Pediatr Hematol Oncol 9:324–330, 1987.
9. Hasle H: Myelodysplastic syndromes in childhood—classification, epidemiology and treatment. Leuk Lymphoma 13:11–26, 1994.
10. Rubin CM, Arthur DC, Woods WG, Lange BJ, Nowell PC, Rowley JD, Nachman J, Bostrom B, Baum ES, Suarez CR, Shah NR, Morgan E, Maurer HS, McKenzie SE, Larson RA, LeBeau MM: Therapy-related myelodysplastic syndrome and acute myeloid leukemia in children: correlation between chromosomal abnormalities and prior therapy. Blood 78:2982–2988, 1991.
11. Gadner H, Haas OA: Experience in pediatric myelodysplastic syndromes. Hematol Oncol Clin North Am 6:655–672, 1992.
12. Baranger L, Baruchel A, Leverger G, Schaison G, Berger R: Monosomy-7 in childhood hemopoietic disorders. Leukemia 4: 345–349, 1990.
13. Uderzo C, Locasciulli A, Cantu-Rajnoldi A, Mozzana R, Lambertenghi-Deliliers G, Masera G: Allogeneic bone marrow transplantation for myelodysplastic syndromes of childhood: report of three children with refractory anemia with excess of blasts in transformation and review of the literature. Med Pediatr Oncol 21:43–48, 1993.
10. Dolan G, Reid MM: Congenital sideroblastic anemia in two girls. J Clin Pathol 44:464–465, 1991.
15. Mecucci C, Van den Berghe H: Cytogenetics of myelodysplastic syndromes. Hematol Oncol Clin North Am 6:523–541, 1992.
16. Schwartz CL, Cohen HJ: Preleukemic syndromes and other syndromes predisposing to leukemia. Pediatr Clin North Am 35:853–871, 1988.